JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 2002, p. 852–856 Vol. 40, No. 3
0095-1137/02/$04.00+0 DOI: 10.1128/JCM.40.3.852–856.2002

Trends in Antifungal Susceptibility of *Candida* spp. Isolated from Pediatric and Adult Patients with Bloodstream Infections: SENTRY Antimicrobial Surveillance Program, 1997 to 2000

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Received 24 September 2001/Returned for modification 2 December 2001/Accepted 12 December 2001

From 1 January 1997 through 31 December 2000, 2,047 bloodstream infections (BSIs) due to *Candida* spp. were reported from hospitals in the United States, Canada, Latin America, and Europe participating in the SENTRY Antifungal Surveillance Program. Among individuals in four age groups (≤1, 2 to 15, 16 to 64, and ≥65 years) *Candida albicans* was the most common species, causing 60, 55, 55, and 50% of infections, respectively. *C. glabrata* caused 17 to 23% of BSIs in those ages 16 to 64 and ≥65 years, whereas it caused only 3% of BSIs in the individuals in the two younger age groups ($P < 0.001$). *C. parapsilosis* (which caused 21 to 24% of BSIs) and *C. tropicalis* (which caused 7 to 10% of BSIs) were more common than *C. glabrata* in individuals ages ≤1 year and 2 to 15 years. Isolates of *Candida* spp. showed a trend of decreasing susceptibility to fluconazole, itraconazole, and amphotericin B with increasing patient age ($P \leq 0.01$). None of the *C. glabrata* isolates from individuals ≤1 year old were resistant to fluconazole, whereas they made up 5 to 9% of isolates from individuals ages 16 to 64 and ≥65 years. Isolates of *C. tropicalis* from patients ≤1 year old were more susceptible to flucytosine (MIC at which 90% of isolates are inhibited [MIC_{90}], 0.5 μg/ml; 0% resistant isolates) than those from patients ≥65 years old (MIC_{90}, 32 μg/ml; 11% resistant isolates). The investigational triazoles posaconazole, ravuconazole, and voriconazole were all highly active against all species of *Candida* from individuals in all age groups. These data demonstrate differences in the species distributions of pathogens and differences in antifungal resistance among isolates from individuals in the pediatric and adult age groups. Ongoing surveillance will enhance efforts to limit the extent of antifungal resistance in individuals in various age groups.

The proliferation of antimicrobial resistance surveillance programs has provided useful information regarding resistance trends, the distribution of pathogens among various countries, and among types of infections (7). Although most surveillance programs have focused on bacterial pathogens, several have provided information on invasive candidiasis as well. A population-based surveillance study conducted by the Centers for Disease Control and Prevention (5), the NEMIS study (2, 9, 16, 19), the SCOPE study (4), and the SENTRY Program (3, 11, 13–15) have all contributed information regarding the species distributions and antifungal susceptibilities of isolates of *Candida* spp. isolated from patients with bloodstream infection (BSIs) over the decade from 1990 to 2000. Although the Centers for Disease Control and Prevention and NEMIS studies provided some information on *Candida* BSIs in both adult and neonatal populations, none of the *Candida* surveillance studies have provided information on the distributions of species or the antifungal susceptibility profiles of pathogens isolated from patients with BSIs stratified according to the age of the patient.

The SENTRY Antifungal Surveillance Program has been active continuously since January 1997 and has reported the specific types of pathogens isolated from more than 2,000 episodes of *Candida* BSIs in 72 medical centers internationally and antifungal susceptibility data for those pathogens (3, 11, 13–15). In the study described in this report, we examined the frequency of pathogen occurrence and the susceptibilities of the various species isolated to both licensed and investigational antifungal agents for individuals in four different age groups: ≤1, 2 to 15, 16 to 64, and ≥65 years.

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MATERIALS AND METHODS

Study design. The SENTRY Antifungal Surveillance Program was established in 1997 and has been described in detail in previous publications (3, 11, 13–15). The present report focuses on BSIs due to *Candida* spp. from U.S., Canadian, Latin American, and European sites. BSIs due to *Candida* spp. were reported from 32 medical centers in the United States, 23 medical centers in Europe, 9 medical centers in Latin America, and 7 medical centers in Canada over the 4-year period from January 1997 through December 2000. The institutions that contributed data or isolates to the study are listed in the Appendix.

Organism identification. All fungal isolates from blood cultures were identified at the participating institutions by the routine method in use at each laboratory. Upon receipt at the monitoring site, the isolates were subcultured onto potato dextrose agar (Remel, Lenexa, Kans.) and CHROMagar *Candida* medium (Hardy Laboratories, Santa Maria, Calif.) to ensure viability and purity. Confirmation of species identification was performed with Vitek and API products (bioMerieux, St. Louis, Mo.), as recommended by the manufacturer, or by conventional methods, as required (22). Isolates were stored as suspensions in water or on agar slants at ambient temperature until needed.

Susceptibility testing. Antifungal susceptibility testing of isolates of *Candida* spp. was performed by the reference broth microdilution method described by the National Committee for Clinical Laboratory Standards (NCCLS) (8). The susceptibilities of the isolates to amphotericin B were determined by use of the

TABLE 1. Species distributions of *Candida* Bloodstream Isolates by age group, SENTRY Program, 1997 to 2000

Species	% of isolates from the individuals in the following age groups (yr [no. of isolates tested]):				
	≤1 (273)[a]	2–15 (124)	16–64 (1,028)	≥65 (622)	Total (2,047)
C. albicans	60[a]	55	55	50	54
C. glabrata	3[b]	3[b]	17	23	16
C. parapsilosis	24[c]	21[c]	12	12	15
C. tropicalis	7	10	11	10	10
C. krusei		4	2	2	2
C. guilliermondii	3	2	1	1	1
C. lusitaniae	2	2	1	1	1
Candida spp.	1	3	1	1	1

[a] $P = 0.007$ compared to those ≥65 years old.
[b] $P < 0.001$ compared to those ages 16 to 64 and ≥65 years.
[c] $P < 0.01$ compared to those ages 16 to 64 and ≥65 years.

Etest (AB BIODISK, Solna, Sweden) and RPMI 1640 agar with 2% glucose (Remel), as described previously (12). Standard powders of fluconazole (Pfizer, Inc., New York, N.Y.), voriconazole (Pfizer), ravuconazole (Bristol-Myers Squibb, Wallingford, Conn.), posaconazole (Schering-Plough, Kenilworth, N.J.), itraconazole (Janssen, Beerse, Belgium), and amphotericin B and flucytosine (Sigma, St. Louis, Mo.) were obtained from the respective manufacturers. The MICs of fluconazole, voriconazole, ravuconazole, posaconazole, itraconazole, and flucytosine were the lowest concentrations at which a prominent decrease (approximately 50%) in turbidity relative to that in the growth control well was observed (8). Amphotericin B MICs determined by the Etest were read after 48 h of incubation at 35°C and were determined to be the concentration at which 100% inhibition of growth occurred, which on the Etest strip was the location where the border of the elliptical inhibition zone intercepted the scale on the strip edge (12). Quality control was ensured by testing the strains recommended by NCCLS (8): *Candida krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019.

Interpretive criteria for susceptibility to fluconazole (MIC, ≤8 μg/ml), itraconazole (MIC, ≤0.12 μg/ml), and flucytosine (MIC, ≤4 μg/ml) were those published by Rex et al. (17) and NCCLS (8). The investigational triazoles posaconazole, voriconazole and ravuconazole have not been assigned interpretive breakpoints. For purposes of comparison and because preliminary pharmacokinetic data indicate that the levels of these agents achievable in serum may range from 2 to 6 μg/ml, depending on the dosing regimen (20), we have used a breakpoint for susceptibility of ≤1 μg/ml for all three agents. Interpretive criteria have not yet been defined for amphotericin B; however for comparison purposes in this surveillance study we have determined isolates that were inhibited by ≤1 μg/ml to be susceptible.

Statistical methods. Comparison of the species distributions or MIC distributions in terms of other factors were made by the chi-square test for categorical variables and the Wilcoxon rank sum text for ordinal variables (MICs). All reported *P* values are two-tailed.

RESULTS AND DISCUSSION

Frequency of occurrence of bloodstream pathogens. During the 4-year study period (January 1997 to December 2000), a total of 2,047 BSIs due to *Candida* spp. were reported by SENTRY participants. Table 1 compares the frequencies of occurrence of the seven most commonly isolated pathogens during the time period of the study. These seven species accounted for 99% of all *Candida* BSIs reported from SENTRY study sites. Overall, the rank order of the top five species was unchanged from year to year. These five species (*C. albicans, C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*) accounted for 97% of all *Candida* BSIs. As described previously (15), the only notable geographic difference in the species distribution among the three continents was a higher frequency of *C. glabrata* as a cause of BSIs in the United States.

Comparing the frequency of isolation of different species by age group, we found identical rank orders for the groups 16 to 64 and ≥65 years of age: *C. albicans* > *C. glabrata* > *C. parapsilosis* > *C. tropicalis* > *C. krusei*. The rank order of the frequency of isolation of different species for the groups ≤1 and 2 to 15 years of age was considerably different from that for the two older age groups. The dominant causes of infections in individuals in the infant and pediatric age groups were *C. albicans* and *C. parapsilosis*, and very few infections were due to *C. glabrata* and *C. krusei*. Although *C. albicans* was the most common species in all age groups, the proportions of BSIs due to this species decreased from 60% in the group ≤1 year of age to 50% in the group ≥65 years of age ($P = 0.007$). *C. glabrata* was the second most common species overall, causing 17 to 23% of BSIs in the groups ages 16 to 64 and ≥65 years. In contrast, *C. glabrata* accounted for only 3% of BSIs in the groups ≤1 year and 2 to 15 years of age ($P < 0.001$ compared to the groups 16 to 64 and ≥65 years of age) and was surpassed by both *C. parapsilosis* (which was the cause of 21 to 24% of BSIs) and *C. tropicalis* (which was the cause of 7 to 10% of BSIs) as causes of infection.

Differences in susceptibilities among isolates from individuals in different age groups to both licensed and investigational antifungal agents. Among the licensed antifungal agents fluconazole, itraconazole, amphotericin B, and flucytosine, the susceptibilities of isolates of *Candida* spp. with increasing patient age ($P \leq 0.01$ for trend). Although flucytosine was active overall against isolates from individuals in all age groups (with 95 to 98% of isolates being susceptible), isolates of *C. tropicalis* from patients ≤1 year of age were more susceptible to this agent (MIC at which 90% of isolates are inhibited [MIC_{90}], 0.5 μg/ml; 0% resistant isolates) than those isolates from patients ≥65 years of age (MIC_{90}, 32 μg/ml; 11% resistant isolates) (data not shown).

Among the licensed and investigational azoles, fluconazole, posaconazole, ravuconazole, and voriconazole were all highly active (96 to 100% of isolates were susceptible) against *C. albicans*, *C. tropicalis*, *C. guilliermondii*, and *C. lusitaniae*, regardless of the age group (Table 2). Although fluconazole appeared to be less active against isolates of *C. glabrata* in those ≤1 year of age (63% of isolates were susceptible) than against isolates from those 16 to 64 years of age (70% of isolates were susceptible) and ≥65 years of age (73% of isolates were susceptible), there were no highly resistant (MIC, ≥64 μg/ml) isolates in those ≤1 year of age, whereas 5 to 9% of isolates from the two older groups were highly resistant. Itraconazole was less active than all of the other azoles tested against all species with the exception of *C. albicans*. Consistent with previous reports (3, 10, 13, 15), all three investigational triazoles were highly active against all species from all age groups with the exception of *C. glabrata* isolates from those in the group 16 to 64 years of age, with 88 to 90% of *C. glabrata* isolates from individuals in that group being susceptible to the three investigational triazoles at ≤1 μg/ml but with 95 to 100% of *C. glabrata* isolates from all other age groups being susceptible to the three agents.

The activities of amphotericin B, as determined by the Etest, against the five species that were the most common causes of BSIs are shown in Table 3. As expected, amphotericin B was the most active agent against *C. albicans* (MIC_{90}, 1 μg/ml). The activities of amphotericin B against the other species were

TABLE 2. Antifungal activities of fluconazole, itraconazole, and investigational azole antifungal agents against 2,029 invasive isolates of *Candida* spp. by patient age group, SENTRY Program, 1997 to 2000

Species (no. of isolates) and antifungal agent	<1 yr			2–15 yr			16–64 yr			>65 yr		
	No. of isolates	MIC_{50}/MIC_{90} (μg/ml)	% Susceptible[a]	No. of isolates	MIC_{50}/MIC_{90} (μg/ml)	% Susceptible	No. of isolates	MIC_{50}/MIC_{90} (μg/ml)	% Susceptible	No. of isolates	MIC_{50}/MIC_{90} (μg/ml)	% Susceptible
C. albicans (1,114)												
Fluconazole	163	0.25/0.5	100	68	0.25/0.5	99	569	0.25/0.5	98	314	0.25/0.5	99
Itraconazole	163	0.03/0.12	95	68	0.03/0.12	97	569	0.03/0.12	95	314	0.03/0.12	97
Posaconazole	163	0.03/0.06	100	68	0.03/0.06	98	569	0.03/0.06	99	314	0.03/0.06	99
Ravuconazole	163	0.01/0.03	100	68	0.01/0.03	98	569	0.01/0.03	99	314	0.01/0.03	99
Voriconazole	163	0.01/0.03	100	68	0.01/0.03	99	569	0.01/0.03	99	314	0.01/0.03	98
C. glabrata (334)												
Fluconazole	8	8/—[b]	63	4	2/—	75	180	8/32	70	142	8/16	73
Itraconazole	8	1/—	13	4	0.25/—	100	180	0.5/2	8	142	0.5/2	6
Posaconazole	8	0.25/—	100	4	0.25/—	100	180	0.5/2	88	142	0.5/1	97
Ravuconazole	8	0.12/—	100	4	0.12/—	100	180	0.25/2	89	142	0.25/0.5	97
Voriconazole	8	0.5/—	100	4	0.06/—	100	180	0.12/1	90	142	0.12/1	95
C. parapsilosis (301)												
Fluconazole	66	0.5/2	100	27	0.5/4	100	125	0.5/2	100	83	0.5/2	100
Itraconazole	66	0.12/0.25	80	27	0.12/0.25	63	125	0.12/0.25	64	83	0.12/0.25	63
Posaconazole	66	0.03/0.12	100	27	0.06/0.12	100	125	0.06/0.12	100	83	0.06/0.12	100
Ravuconazole	66	0.03/0.06	100	27	0.03/0.06	100	125	0.03/0.06	100	83	0.03/0.06	100
Voriconazole	66	0.03/0.06	100	27	0.03/0.06	100	125	0.03/0.06	100	83	0.03/0.12	100
C. tropicalis (209)												
Fluconazole	20	0.5/1	100	13	0.5/2	100	113	0.5/2	96	63	0.5/1	100
Itraconazole	20	0.12/0.25	70	13	0.12/0.5	62	113	0.12/0.5	68	63	0.12/0.25	67
Posaconazole	20	0.03/0.12	100	13	0.03/0.12	100	113	0.03/0.12	99	63	0.03/0.25	100
Ravuconazole	20	0.03/0.06	100	13	0.03/0.12	100	113	0.03/0.12	97	63	0.03/0.12	100
Voriconazole	20	0.06/0.12	100	13	0.03/0.06	100	113	0.03/0.12	97	63	0.03/0.12	100
C. krusei (39)												
Fluconazole				5	16/—	20	23	32/64	9	11	32/64	9
Itraconazole				5	0.25/—	40	23	0.5/2	0	11	1/2	9
Posaconazole				5	0.5/—	100	23	0.25/0.5	100	11	0.25/0.5	100
Ravuconazole				5	0.25/—	100	23	0.25/0.5	95	11	0.5/0.5	100
Voriconazole				5	0.12/—	100	23	0.25/1	100	11	0.5/1	100
C. guilliermondii (14)												
Fluconazole	6	2/—	100	2	2/—	100	5	2/—	100	1	>64	0
Itraconazole	6	0.25/—	0	2	0.12/—	50	5	0.25/—	40	1	>4	0
Posaconazole	6	0.12/—	100	2	0.06/—	100	5	0.06/—	100	1	>8	0
Ravuconazole	6	0.25/—	75	2	0.03/—	100	5	0.06/—	100		>8	0
Voriconazole	6	0.06/—	100	2	0.03/—	100	5	0.06/—	100	1	>8	0
C. lusitaniae (18)												
Fluconazole	7	0.25/—	100	2	0.25/—	100	6	0.25/—	100	3	0.5/—	67
Itraconazole	7	0.12/—	71	2	0.06/—	50	6	0.12/—	50	3	0.25/—	33
Posaconazole	7	0.03/—	100	2	0.03/—	100	6	0.03/—	100	3	0.03/—	100
Ravuconazole	7	0.03/—	100	2	0.03/—	100	6	0.03/—	100	3	0.03/—	67
Voriconazole	7	0.03/—	100	2	0.01/—	100	6	0.01/—	100	3	0.01/—	100

[a] Percent susceptible at MIC of ≤8 μg/ml (fluconazole), ≤0.12 μg/ml (itraconazole), or ≤1 μg/ml (all other agents).
[b] —, MIC_{90} was not calculated when the number of isolates tested was <10.

significantly less ($P < 0.001$) than that observed against *C. albicans*: MIC_{90} for *C. glabrata*, 4 μg/ml; MIC_{90} for *C. parapsilosis*, 4 μg/ml; MIC_{90} for *C. krusei*, 8 μg/ml. Although in our hands the Etest tended to give higher amphotericin B MICs for the non-*C. albicans* species than for *C. albicans*, the same tendency was seen with the NCCLS microdilution method when it was applied to a subset of 1,077 isolates (data not shown). Notably, 17.4% of *C. glabrata* isolates and 27.8% of *C. krusei* isolates appeared to be resistant (MICs, ≥2 μg/ml) when they were tested by the NCCLS method. As reported previously (12), the level of agreement between the results of the Etest and those of the broth microdilution method was excellent (98.7% within 2 $\log_2$ dilutions).

TABLE 3. Antifungal activities of amphotericin B against 1,997 invasive isolates of *Candida* spp., SENTRY, Program, 1997 to 2000

Species	No. of isolates tested	Cumulative % inhibited at MIC (μg/ml) of[a]:									
		0.06	0.12	0.25	0.5	1	2	4	8	16	32
C. albicans	1,114	0.2	0.4	2.7	38.2	92.1	99.5	100	100	100	100
C. glabrata	334	0.6	0.9	1.8	5.7	41.4[b]	83.3	97.9	99.7	100	100
C. parapsilosis	301	0.0	0.0	0.3	2.7	44.1[b]	80.9	97.0	99.3	100	100
C. tropicalis	209	0.0	0.0	0.5	8.1	48.8[b]	90.9	99.5	100	100	100
C. krusei	39	0.0	0.0	0.0	0.0	10.3[c]	43.6	82.1	97.4	100	100

[a] Amphotericin B MICs were determined by the Etest (overall agreement with the broth microdilution method, 98.7%).
[b] $P < 0.001$ compared to the results for *C. albicans*.
[c] $P < 0.001$ compared to the results for each other species group.

It appears that the differences in susceptibility to amphotericin B and the azoles among the isolates from individuals in four age groups may be largely due to differences in the species distributions among individuals in the younger age groups compared to those among individuals in the older age groups. The groups ≤1 year and 2 to 15 years of age were predominantly infected with *C. albicans* and *C. parapsilosis*, both of which were considerably more susceptible than *C. glabrata* to the antifungal agents tested. Individuals in the older age groups, and particularly those ≥65 years old, had relatively fewer infections due to *C. albicans* and significantly more infections due to *C. glabrata* than individuals in the younger age groups. The decreased susceptibilities of *C. glabrata* to both the azoles and amphotericin B are evident in Tables 2 and 3 and accounted for the differences in susceptibilities among the isolates from individuals in the different age groups.

The predominance of *C. albicans* and *C. parapsilosis* as the etiologic agents of fungemia in neonates has previously been noted by Kao et al. (5) and Saiman et al. (19), among others; however, the lack of infections with *C. glabrata* and *C. krusei* in this age group is less well appreciated. The increasing importance of *C. glabrata* in the adult population is well known, and the proportion of BSIs due to *C. glabrata* has been noted to be considerably higher in individuals >60 years of age in some institutions (6, 15). The reasons for these differences are speculative but may relate to the tendency for neonatologists and pediatricians to use amphotericin B preferentially over fluconazole in the treatment of documented or suspected candidemia (18) and the pervasive use of fluconazole in the adult hospital population (1). Furthermore, vertical transmission of *C. albicans* from mother to infant and horizontal transmission of *C. parapsilosis* from patient to patient in the neonatal intensive care unit environment are well documented and may also account for the predominance of these two species in infants and children (9, 21).

Summary and conclusions. Antifungal resistance surveillance programs provide important information both for the development of recommendations for empirical antifungal therapy and for the design of programs for the control of antifungal resistance. The present study demonstrates differences in the spectrum of pathogens and in antifungal susceptibilities among isolates from individuals in the pediatric and adult age groups in the SENTRY Program. The most notable trends were those of a decreasing frequency of occurrence of *C. albicans* and an increasing frequency of occurrence of *C. glabrata* with increasing patient age.

Decreased susceptibilities to fluconazole, itraconazole, and amphotericin B were most prominent among *C. glabrata* and *C. krusei* isolates from individuals in all age groups. Ongoing surveillance is essential and will enhance efforts to limit the extent of resistance among isolates from individuals in the various age groups.

APPENDIX

Participating institutions contributing data or isolates to the study included The Medical Center of Delaware, Wilmington (L. Steele-Moore); Clarion Health Methodist Hospital, Indianapolis, Ind. (G. Denys); Henry Ford Hospital, Detroit, Mich. (C. Staley); Summa Health System, Akron, Ohio (J. R. Dipersio); Good Samaritan Regional Medical Center, Phoenix, Ariz. (M. Saubolle); Denver General Hospital, Denver, Colo. (M. L. Wilson); University of New Mexico Hospital, Albuquerque (G. D. Overturf); University of Illinois at Chicago (P. C. Schreckenberger); University of Iowa Hospitals and Clinics, Iowa City (R. N. Jones); Creighton University, Omaha, Nebr. (S. Cavalieri); Froedtert Memorial Lutheran Hospital-East, Milwaukee, Wis. (S. Kehl); Boston Veterans Affairs Medical Center, Boston, Mass. (S. Brecher); Columbia Presbyterian Medical Center, New York, N.Y. (P. Della-Latta); Long Island Jewish Medical Center, New Hyde Park, N.Y. (H. Isenberg); Strong Memorial Hospital, Rochester, N.Y. (D. Hardy); Kaiser Regional Laboratory, Berkeley, Calif. (J. Fusco); Sacred Heart Medical Center, Spokane, Wash. (M. Hoffmann); University of Washington Medical Center, Seattle (S. Swanzy); Barnes-Jewish Hospital, St. Louis, Mo. (P. R. Murray); Parkland Health & Hospital System, Dallas, Tex. (P. Southern); The University of Texas Medical School, Houston (A. Wanger); University of Texas Medical Branch at Galveston, Galveston, Tex. (B. Reisner); University of Louisville Hospital, Louisville, Ky. (J. Snyder); University of Mississippi Medical Center, Jackson (J. Humphries); Carolinas Medical Center, Charlotte, N.C. (S. Jenkins); University of Virginia Medical Center, Charlottesville (K. Hazen); University of Alberta Hospital, Edmonton, Alberta, Canada (R. Rennie); Health Sciences Centre, Winnipeg, Manitoba, Canada (D. Hoban); Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada (K. Forward); Ottawa General Hospital, Ottawa, Ontario, Canada (B. Toye); Royal Victoria Hospital, Montreal, Quebec, Canada (H. Robson); Microbiology Laboratory, C.E-.M.I.C., Buenos Aires, Argentina (J. Smayvsky); Hospital San Lucas and Olivos Community Hospital, Buenos Aires, Argentina (J. M. Casellas and G. Tome); Lamina LTDA, Rio De Janeiro, Brazil (J. L. M. Sampaio); Unidad De Microbiologia Oriente, Santiago, Chile (V. Prado); Hospital Clinico Universidad Catolica, Santiago, Chile (E. Palavecino); Corp. Para Investigaciones Biologicas, Medellin, Colombia (J. A. Robledo); Instituto Nacional de la Nutricion, Mexico City, Mexico (J. S. Osornio); Laboratorio Medico Santa Luzia, Florianopolis, Brazil; Instituto DE Doencas Infecciosas-IDIPA, Sao Paulo, Brazil (H. S. Sader); Centro Medico De Caracas, San Bernadino, Caracas, Venezuela (M. Guzman); Chru De Lille Hopital Calmette, Lille, France (M. Roussel-Delvallez); National University of Athens Medical School, Athens, Greece (N. Legakis); Sheba Medical Center, Tel-Hashomer, Israel (N. Keller); University Hospital V. de Macarena, Seville, Spain (E. J. Perea); Hospital de Bellvitge, Barcelona, Spain (J. Linares); Hospital Ramon y Cajal, Madrid, Spain (R. Canton); Unite de Bacteriologie, Luasanne, Switzerland (F. Praplan); Hacettepe Universitaesi Tip Fakultesi, Ankara, Turkey (D. Gur); Universita degli Studi di Genova, Genoa, Italy (E. Debbia); Azienda Policlinico University Catania, Catania, Italy (G. Nicoletti); Policlinico Agostino Germelli, Rome, Italy (G. Fadda); Universitat Bonn, Bonn, Germany (K. P. Schaalb); J.-W.-Goethe Universitat, Frankfurt, Germany (P. Shah); University Hospital, Linkoping, Sweden (H. Hanberger); Sera & Vaccines Central Research Laboratory, Warsaw, Poland (W. Hryniewicz); St. Thomas Hospital, London, United Kingdom (G. French); Universite Libre de Bruxelles-Hopital Erasme, Brussels, Belgium (M. J. Struelens); and Marmara Universitesi Tip Fakultesi, Istanbul, Turkey (V. Korten).

ACKNOWLEDGMENTS

This study was supported in part by research grants from Bristol-Myers Squibb (SENTRY), Pfizer Pharmaceuticals, and Schering-Plough Research Institute.

Linda Elliott provided excellent support in the preparation of the manuscript. We express our appreciation to all SENTRY site participants.

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